REMARKS

In the teleconference held January 14, 2010 and summarized in Examiner's **Interview Summary** of January 19, 2010: "(1) Applicant argued that coenzyme Q10 and N-acetylcysteine are not functionally equivalent. (2) Applicant argues that the transcriptional regulatory factor NF-kB is not linked to hyperlipidemia. (3) Applicant argues that the state of the art exits such that CLA is not known to treat hyperlipidemia. (4) Applicant will provide a Declaration showing a side by side comparison that coenzyme Q10 and N-acetylcysteine are not functionally equivalent. Applicant will present arguments supporting these assertions in a RCE. (5) Potential claim amendments limiting the scope of the invention were also discussed to advance prosecution." (Numbering of points was added by Applicant)

Applicants respond to each of these points thusly

(1) Coenzyme Q10 and N-acetylcysteine are not functionally equivalent - The applicant has previously indicated that CoQ10 is ***lipid soluble*** and NAC is ***water-soluble***, such major physical differences, which are supported by structural differences (see below) factually preclude functional equivalence. There exists **no** research to support the fact that NAC and CoQ10 are equivalent in their antioxidant activity in vitro or in vivo. Data generated by the applicant prior to the filing of the instant application support other publish research on the nonequivalence of the two compounds (see Response 4).

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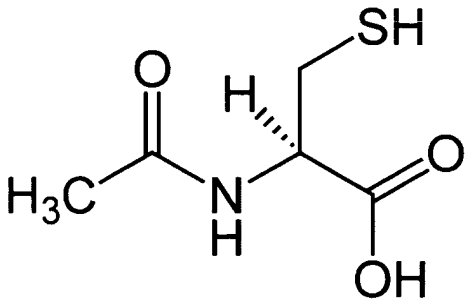
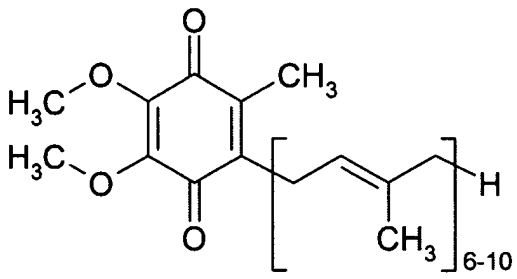


N-Acetylcysteine



CoQ10

Examples of categories in which do not provide *prima facie* evidence of equivalence:

1. Peptides of similar length, but different amino acid composition are not functionally equivalent.
2. Within the class of amino acids, not all amino acids are functionally equivalent (e.g. NAC and cysteine are not functionally equivalent).
3. D- and L-amino acids are not functionally equivalent.
4. Structurally NAC and CoQ10 are not members of the same genus.

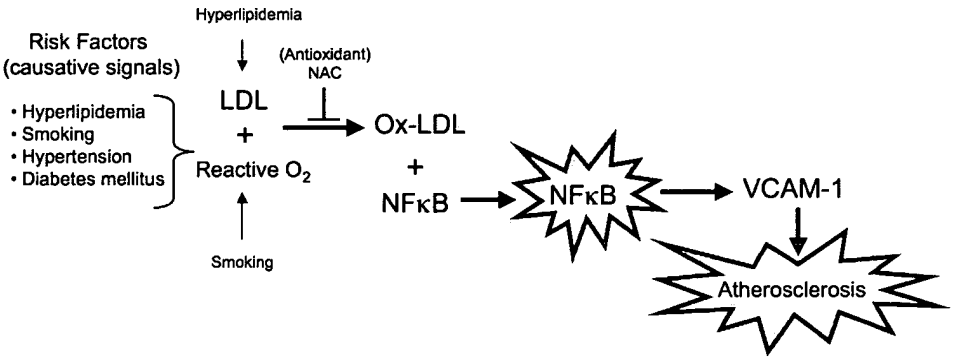
As noted in MPEP 2141.01(a), "While Patent Office classification of references and the cross-references in the official search notes of the class definitions are some evidence of "nonanalogy" or "analogy" respectively, the court has found "the similarities and differences in structure and function of the inventions to carry far greater weight." In re Ellis, 476 F.2d 1370, 1372, 177 USPQ 526, 527 (CCPA 1973)." The extreme differences in structure of NAC and CoQ10 do not support or lend evidence of functional equivalence.

(2) Nuclear Factor-kappa B (NF-kB) is not linked to hyperlipidemia – The lack of linkage between NF-kB and hyperlipidemia as discussed in the teleconference of 14 January 2010 was limited to the teachings of Medford. In this regard, Medford teaches treatment of cardiovascular diseases and non-cardiovascular inflammatory diseases that are ***mediated by VCAM-1*** (ABSTRACT). In the model described by Medford and illustrated in Figure 1, the

inhibition of NF-kB activation is dependant on the inhibition of ox-LDL (not LDL) production by an antioxidant in VCAM-1 expressing endothelial cells.

As noted in the teleconference, a prior art ***reference must be considered in its entirety***, i.e., as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). To combine references without ***evidentiary support***, or at least some suggestion or motivation, by the prior art constitutes impermissible hindsight. Distilling an invention down to the "gist" or "thrust" of an invention disregards the requirement of analyzing the subject matter "as a whole." W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984)

Figure 1. A schematic representation of the link between hyperlipidemia and activation of nuclear factor kappa B (NF-kB) in endothelial cells expressing VCAM-1 as described by Medford [Col 2, lines 6-11].



Taken in its entirety, Medford teaches the use of NAC in VCAM-1 expressing cells only (endothelial cells) while hepatocytes, which synthesis the LDL, are epithelial cells that do not express VCAM-1. Hyperlipidemia is the result of biosynthesis of LDL in hepatocytes. The only compounds capable of effectively reducing serum lipids (hyperlipidemia) function in the small intestine to inhibit the absorption of cholesterol (e.g. phytosterols, cholestyramine) or in the

liver to inhibit the biosynthesis of LDL (HMG-CoA reeducates inhibitors).

Further, the only response variable listed by Medford is VCAM-1 expression. Thus, redox activation of NF-kB in VCAM-1 expressing cells as taught by Medford is not in any way linked to hyperlipidemia. Figure 2 illustrates the teaching of Medford.

It is clear that the teaching of Medford is related in its entirety to VCAM-1 expressing cells and it was known by those trained in the art that hepatocytes, which synthesize LDL, do not express VCAM-1.

Figure 2. Role of Ox-LDL (Modified LDL) in the expression of adhesion molecules on the surface of endothelial cells, attachment of monocytes and T cells to the adhesion molecules, and the development of atherosclerotic plaques.

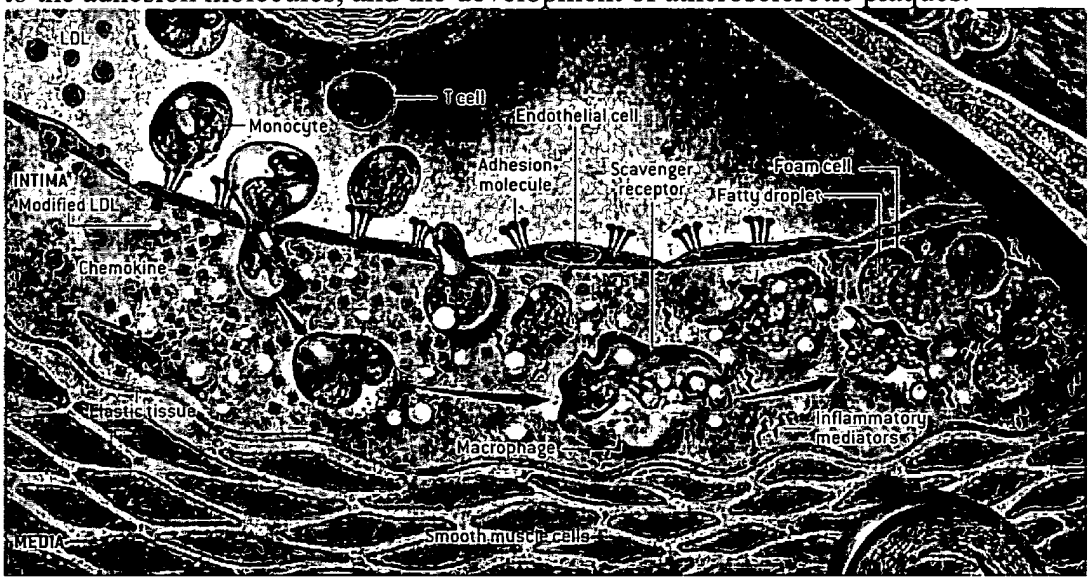


Figure from Libby, P., Atherosclerosis: the new view. *Sci Am* **2002,** *286* (5), 46-55.

(2) ***CLA is not known to treat hyperlipidemia*** - At the time of the claimed invention seven of eight published clinical studies indicated a lack of effect of CLA on lowering blood lipids [reviewed in Larsen, T. M., Toubro, S., and Astrup, A. Efficacy and safety of dietary supplements containing CLA for the treatment of obesity: evidence from animal and human studies. *J Lipid Res* **2003**, *44*, 2234-41]. The authors

of this review conclude, "the evidence from human, short-term studies suggest that CLA supplementation **does not reduce body fat or increase fat-free mass.** There is evidence that CLA isomers sold as dietary supplements have marked biological effects, but there is accumulating evidence that the CLA t10,c12 isomer may adversely influence human health by **producing lipodystrophy** and insulin resistance." Thus, it was the consensus of those trained in the art at the time of the filing of the instant application that CLA was not an effective treatment for hyperlipidemia.

The Examiner's argues (Office Action letter 12/8/09) that the above reference was not convincing in light of the fact that no long term clinical trials were conducted and one of the seven trials (14%) reported appeared to have a positive effect for CLA reducing serum triglycerides. This argument is specious in that it is highly unlikely that long-term trials would be conducted when the probability of failure is nearly 85%. Clearly, the weight of clinical evidence that existed at the time of the instant application indicated a lack of effect of CLA on hyperlipidemia and was represented by a published consensus.

(4) Applicant will provide a Declaration showing a side-by-side comparison that coenzyme Q10 and N-acetylcysteine are not functionally equivalent – The attached Declaration describes a series of studies conducted by the Applicants in the period prior to the instant application. Based upon whole cell studies in oxidant-stressed Jurkat, RAW 264.7 and HAEC cells, NAC and CoQ10 were not functionally equivalent anti-oxidants and this was known to the Applicants prior to the filing of the referenced application.

Note also that the HACE cells used by the Applicants, where NAC demonstrated highly active anti-oxidant activity (9.9 μg/mL) and CoQ10 was inactive, was the same cell line used in Medford. Thus, it would not be obvious

for the Applicants to substitute CoQ10 for NAC as functionally equivalent anti-oxidants, as the Applicants knew these two compounds were not functionally equivalent prior to the instant application.

(5) Potential claim amendments limiting the scope of the invention were also discussed to advance prosecution - Pursuant to the January teleconference and consistent with its discussion points, Claim 21 was amended to read:

> A method for treating, or normalizing subcutaneous fat loss resulting from anti-retroviral treatment of HIV-1 infection in a subject in need thereof comprising: administering to said subject a pharmaceutically effective dose of ~~a~~ conjugated ~~fatty~~ linoleic acid in combination with a pharmacologically effective dose of N-acetylcysteine in a ratio of about 14:1 to 1:14.

Further Claims 22, 23 and 24 were withdrawn. Claim 31 was amended to read:

> A method for treating or normalizing hyperlipidemia coincident with subcutaneous fat loss and body wasting resulting from anti-retroviral treatment of HIV-1 infection in a subject in need thereof comprising: administering to said subject a pharmaceutically effective dose of ~~a~~ conjugated ~~fatty~~ linoleic acid in combination with a pharmacologically effective dose of N-acetylcysteine in a ratio of about 14:1 to 1:14.

And Claims 33, 34 and 35 were withdrawn. Examples presented in the instant application support the limiting ratios.

SUMMARY

In view of the foregoing, the Applicants assert that the current application claims present allowable subject matter and the allowance thereof is requested. If any impediment to the allowance of these claims remains after consideration of the present amendment and above remarks, and such impediment could be

removed during a telephone interview, the Examiner is invited to telephone Dr. John G. Babish so that such issues may be resolved as expeditiously as possible.

Dated this 8th day of March 2010.

Respectfully submitted,
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